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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1637	13

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,113	EVANS ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,10,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Claims 1-18 are pending.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843).

Patel teaches a method of determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism and a second nucleotide

polymorphism separated by at least 200 nucleotides (see abstract and 3563, figure 2 which shows 1.1 kb fragment with polymorphims at each end) comprising:

(a) obtaining a DNA sample from a human source comprising said contiguous DNA segment (page 3562, subheading "DNA extraction"),

(b) using said DNA sample as a template to form a product which is capable of being subject to intramolecular ligation (page 3562, subheading "Inverse PCR),

(c) ligating the ends of the DNA fragment to each other so as to produce a circular DNA molecule (page 3562, subheading "Inverse PCR"),

(d) determining the haplotype of the first and second nucleotide polymorphism by allel specific PCR amplification (page 3562, subheading "Inverse PCR").

Patel further teaches that the method can be applied to sequences up to 10 kb apart and suggests that even larger regions can be used (page 3567, column 1, lines 6-9).

Patel teaches mutations which are substitutions of single nucleotides and where there are a series of nucleotide polymorpisms located between the two amplified polymorphisms (see page 3561, column 2 and page 3562, figure 1).

Patel teaches determing the presence of multiple different polymorphisms (see page 3565, column 1, subheading "Double ARMS Inverse PCR (DARMSI-PCR)".

Patel teaches amplification and detection of each haplotype in the same gene, the globin cluster (page 3562, figure 1).

Patel further teaches that the method can be used for diagnostic purposes (see page 3567, column 1).

Patel does not teach preparation of the template for intramolecular ligation by long range PCR.

Michalatos-Beloin teaches haplotyping methods where the molecules are prepared by long range PCR (page 4842, figures 2 and 3). Michalatos-Beloin also teaches that amplification of up to 40 kb should be possible (see page 4843 (listed as page 4867), column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the long range PCR method of Michalatos-Beloin to prepare the sample for the haplotyping method of Patel since Michalatos-Beloin states "The allele-specific long range PCR products were used as templates for amplification of the STR (page 4867, column 1)". An ordinary practitioner would have been motivated to use long range PCR as the template for the DARMSI-PCR method of Patel rather than genomic DNA in order to permit improved discrimination and detection as taught by Michalatos-Beloin (see page 4867, column 2) and since Michalatos-Beloin notes "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications (page 4867, column 2). Thus, application of the method of Michalatos-Beloin to the inverse PCR method of Patel can be used to increase the accuracy of the Patel method.

4. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al

(Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16 and further in view of Krynetski et al (Proc. Natl. Acad. Sci. (1995) 92:949-953).

Patel in view of Michalatos-Beloin teach the limitations of claims 1-16 as discussed above. Patel in view of Michalatos-Beloin do not teach application of the method to the TPMT gene.

Krynetski teaches that there are two haplotypes in the TPMT gene, one of which is associated with cytotoxicity in chemotherapeutic treatment using methylmercaptopurine (see page 949, columns 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Patel in view of Michalatos-Beloin to haplotype the TPMT gene since Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic dosages of mercaptopurine (page 949, column 2)". Thus, an ordinary practitioner would have been motivated to haplotype the TPMT gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are TPMT deficient prior to toxic treatment.

5. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al

(Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16 and further in view of Martin et al (Am. J. Hum. Genet. (2000) 67:383-394).

Patel in view of Michalatos-Beloin teach the limitations of claims 1-16 as discussed above. Patel in view of Michalatos-Beloin do not teach application of the method to the listed genes.

Martin teaches haplotype analysis of the ApoE gene in order to analyze the presence of Alzheimer's disease (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Patel in view of Michalatos-Beloin to haplotype the ApoE gene since Martini teaches "Haplotype analysis using family data increased significance over that see in single-locus tests for some of the markers, and for these data, improved localization of the gene (abstract)." Thus, an ordinary practitioner would have been motivated to haplotype the ApoE gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are at risk for Alzheimer's disease.

Response to Arguments

6. Applicant's arguments filed November 13, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation to combine is provided in the rejection. The rejection expressly notes that An ordinary practitioner would have been motivated to use long range PCR product as the template for the DARMSI-PCR method of Patel rather than genomic DNA in order to permit improved discrimination and detection as taught by Michalatos-Beloin (see page 4867, column 2) and since Michalatos-Beloin notes "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications (page 4867, column 2). "

Thus, the motivation is to improve the accuracy of the method by using a superior source of target nucleic acid.

Applicant indicates that no support was found for the teaching of Michaelos-Beloin to improve discrimination and detection. On page 4867 (which the examiner notes is probably a typo by the journal, since the previous page is 4842), regarding improved discrimination, Michaelos-Beloin states "Molecular haplotyping will allow

characterization and discrimination of many configurations of markers (page 4867, column 2). This is an express statement that the method will improve the discrimination of many configurations of markers. Regarding detection, Michaelos-Beloin states "Molecular haplotypes derived from markers of different structure, mutation rate and heterozygosity in regional or ethnic populations will provide a rich source of data for many endeavors (page 4867, column 2)." This is an express statement that the method will improve detection in a variety of different populations.

The citation from page 4867, column 2 by Applicant does not indicate that the method could detect all haplotypes but is clearly dependent upon the first sentence which states "A molecular haplotyping approach similar to our CD4 work could be based on different kinds of polymorphic markers (see page 4867, column 2)'. Michaelos-Beloin is simply identifying different types of markers and noting that some are better than others.

Applicant then argues that the teaching of a benefit by Michaelos-Beloin that the use of Long-range PCR teaches away. To the contrary, this is an express suggestion of the utility of long range PCR in a variety of haplotyping methods, including the method of Patel et al. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply

because Michaelos-Beloin had a preferred embodiment, this embodiment does not prevent the use of alternative embodiments or constitute a teaching away from such embodiments such as the use of combination with Patel.

Similiarly, the argument that Patel teaches away is also unavailing, since Patel simply teaches a preferred embodiment. Patel has no teaching or suggestion that longer range methods would not work or are undesirable.

Applicant then argues that the combination of the methods would render the invention inoperable. Here, Applicant fails to properly combine the methods. The only element lacking from Patel is the use of long range PCR. In combining Michaelos-Beloin with Patel, the only element which Patel requires in order to perform the long range haplotyping is the long range PCR. Thus, the combination is operable and would have a reasonable expectation of success.

Consequently, the prima facie case of obviousness has not been overcome, nor rebutted.

Applicant argues the remaining 103 rejections are overcome because the primary rejection is overcome. Since the primary rejection is maintained, these arguments are not found persuasive.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

December 13, 2002